# Multidimensional assessment of diastolic dysfunction using echocardiography and magnetic resonance imaging in acute coronary syndrome


**AZARISMAN SHAH MOHD SHAH**

**MBBS MMED**


**DOCTOR OF PHILOSOPHY**


**DISCIPLINE OF MEDICINE**

**SCHOOL OF MEDICINE**

**UNIVERSITY OF ADELAIDE**

**ADELAIDE, SOUTH AUSTRALIA**

**AUSTRALIA**


Submitted in the total fulfilment of the requirements

for the degree of Doctor of Philosophy

December 2014

# DECLARATION

I performed the research presented in this thesis within the Department of Medicine, University of Adelaide, Adelaide, Australia. This work contains no material that has been accepted for the award of any other degree or diploma in any other university or institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

Dr Azarisman Shah Mohd Shah
University of Adelaide
Adelaide
South Australia 5000
AUSTRALIA

*To Aszrin, my dear wife and my children Ameera, Asma', A'isha, Ayman,*
*'Ammar and 'Abdullah 'Aqeel for whom this work is dedicated and*
*without whom, I am but a rudderless ship, adrift*
*in the vast emptiness of the sea.*

# TABLE OF CONTENTS

# ACKNOWLEDGEMENTS

I am thankful to *Allâh* first and foremost for making this journey possible and keeping me sane throughout the entire time. True are the words "*Whosoever puts his faith in Allâh and keeps his duty to Him, Allâh will make a way for him out of every difficulty. And Allâh will provide him from (sources) he never could imagine. And whosoever puts his trust in Allâh, then He will suffice him*" (Qur'an 65:2-3). Despite the myriad of challenges and difficulties, especially with trying to juggle clinical duties in a busy Clinical Fellowship in Cardiovascular Magnetic Resonance Imaging whilst trying to conduct a PhD research and looking after the welfare of a family of 8 so far from home and support, we have managed to prevail,….somehow.

A large measure of gratitude is reserved for Professor Stephen Worthley who provided a huge degree of vision and support for the whole project and ensured that the research kept plugging on despite the myriad of challenges. I am deeply indebted also for his patience and forbearance in facilitating my research, our family's wellbeing and my clinical training. I am truly fortunate to have met his acquaintance and benefitted from his guidance and example as a clinician and mentor.

To my co-supervisors, Associate Professor Dr Matthew Worthley and Dr Karen Teo, thank you for your guidance and limitless accessibility. I have certainly benefitted from the training and camaraderie that you have so willingly offered and I hope that I could continue to rely on your help and guidance for a long time to come. To Mr Angelo Carbone, Ms Kerry Williams, Mr Ben Koschade, Mr Michael Cursaro and Mr Vince Schirripa, you have all been the bedrock upon which my research stood. Thank you for your kind accommodation, consistent support and constant willingness to go the extra mile for me.

I would also like to thank my many colleagues at the Cardiovascular Research Centre of the Royal Adelaide Hospital especially Dr Dennis Wong, Dr Angela Bertaso and Dr James Richardson for their guidance, camaraderie and support throughout the entire period. I would like to thank the Ministry of Science Technology and Innovation, Malaysia (MOSTI) for the scholarship to pursue this dream, the Management Services Division, International Islamic University Malaysia for facilitating it and my colleagues at the Department of Internal Medicine, Faculty of Medicine for their kind support and encouragement.

Last but not least, to my dad who left us just as I was starting the Fellowship and PhD, my mom who has been an unwavering pillar upon which I relied upon most of my life and my wife, my best friend, my love and my comfort. Thank you all, may I get the chance to repay you in kind for all your sacrifices, love, support and encouragement, be it in this life or the next.

# THESIS RELATED PUBLICATIONS

## *Original Research*

Azarisman SM, Wong DT, Richardson JD, Li A, Nelson AJ, Shirazi M, Bradley J, Teo KS, Worthley MI, Worthley SG. Evaluation of mitral inflow velocity profile: optimal through plane location for mitral inflow assessment with cardiac magnetic resonance. Experimental and Clinical Cardiology 2014; Volume 20, Issue 1: Pages 975-1001

Azarisman SM, Shirazi M, Bradley J, Teo KS, Worthley MI, Worthley SG. Assessment of diastolic dysfunction in patients with acute coronary syndrome and preserved systolic function: head-to-head comparison between doppler transthoracic echocardiography and velocity-encoded cardiac magnetic resonance. Acta Cardiologica 2015 (in press)

Azarisman SM, Carbone A, Shirazi M, Bradley J, Teo KS, Worthley MI, Worthley SG. Characterisation of myocardial injury via T1 mapping in early reperfused myocardial infarction and its relationship with global and regional diastolic dysfunction. Heart, Lung and Circulation 2015 (in press)

## *Related Work*

Azarisman SM, Teo KS, Worthley MI, Worthley SG.The Role of cardiovascular magnetic resonance in assessment of patients with acute coronary syndrome. World Journal of Cardiology 2014; Volume 6, Issue 6: Pages 405-414 (Invited Review)

Azarisman SM, Teo KS, Worthley MI, Worthley SG. Cardiac magnetic resonance assessment of diastolic dysfunction in acute coronary syndrome. Cardiology in Review (in press)

# THESIS RELATED ABSTRACTS

Azarisman SM, Li A, Richardson JD, Wong DT, Chua SK, Cursaro M, Schirripa V, Williams K, Koschade B, Shirazi M, Bradley J, Teo K, Worthley M, Worthley SG. Optimal planimetry location for MRI-derived mitral inflow velocity assessment of diastolic function. *16th Annual Society of Cardiac Magnetic Resonance Scientific Sessions, San Francisco, 31 January - 3 February 2013.*
[Azarisman et al. J Cardiovasc Magn Reson 2013, 15(Suppl 1):P90]

Azarisman SM, Li A, Wong DT, Richardson JD, Chua SK, Samaraie L, Sidharta SL, Glenie T, Williams K, Koschade B, Teo K, Worthley M, Worthley SG. Tissue injury characterization by pre-contrast T1 mapping post myocardial infarction. *16th Annual Society of Cardiac Magnetic Resonance Scientific Sessions, San Francisco, 31 January - 3 February 2013.*
[Azarisman et al. J Cardiovasc Magn Reson 2013, 15(Suppl 1):E33]

Azarisman S, Richardson J, Wong D, Samaraie L, Cursaro M, Schirripa V, Williams K, Koschade B, Shirazi M, Bradley J, Teo K, Worthley M, Worthley S. Mitral Leaflet Planimetry Location for MRI-derived Mitral Inflow Velocity Assessment of Diastolic Function is the Most Reproducible Method. *61st Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand, Gold Coast, August 2013.*
[Azarisman et al. Heart Lung Circ 2013, 22(S126–S266):445]

Azarisman S, Li A, Wong D, Richardson J, Samaraie L, Williams K, Koschade B, Teo K, Worthley M, Worthley S. Remote Myocardium Characterisation by Pre-contrast T1 and T2* Mapping Post Myocardial Infarction. *61st Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand, Gold Coast, August 2013.*
[Azarisman et al. Heart Lung Circ 2013, 22(S126–S266):463]

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| CAD | Coronary artery disease |
| CE | Cardiac enzyme |
| CMR | Cardiac magnetic resonance imaging |
| CT | Computed tomography |
| CTCA | Computed tomography coronary angiogram |
| CVD | Cardiovascular disease |
| DD | Diastolic dysfunction |
| DT | Deceleration time |
| ECG | Electrocardiography / Electrocardiogram |
| FFR | Fractional-flow reserve |
| FISP | Fast Imaging with Steady-State Precession |
| HLA | Horizontal long axis |
| IQR | Interquartile ranges |
| LA | Left atrium |
| LGE | Late gadolinium enhancement |
| LV | Left ventricular |
| LVEDP | Left ventricular end-diastolic pressure |
| LVEF | Left ventricular ejection fraction |
| LVOT | Left ventricular outflow tract |
| MDCT | Multi-detector computed tomography |
| MV | Mitral valve |
| MI | Myocardial infarction |
| MPI | Myocardial perfusion imaging |
| MVO | Microvascular obstruction |
| NSTEMI | non-ST-segment elevation myocardial infarction |
| PC | Phase contrast |
| PET | Positron emission tomography |
| PV | Pulmonary vein |
| ROI | Regions of interest |
| SPECT | Single-photon emission computed tomography |
| SSFP | Steady-state free precession |

| | |
|---|---|
| STEMI | ST-segment elevation myocardial infarction |
| STIR | Short tau inversion recovery |
| TDI | Tissue Doppler imaging |
| TM | Transmitral |
| T2W | T2-weighted imaging |
| TTE | Transthoracic echocardiography |
| VLA | Vertical long axis |

## SYNOPSIS

Cardiovascular disease (CVD) is the leading cause of death in the western world and is becoming more important in the developing world. Recent advances in diagnosis, revascularisation and pharmacotherapy have resulted in a reduction in mortality. Nevertheless, the burden of disease remains large resulting in high healthcare costs. This has necessitated the introduction of a reliable, non-invasive and cost-effective imaging modality which has the ability to accelerate the diagnosis of acute coronary syndrome (ACS), aid in the risk stratification of de novo coronary artery disease (CAD) and afford incremental information of prognostic value such as viability.

Clinically, the realm of ACS assessment has always been dependent on conventional methods such as electrocardiography (ECG) and serological markers of infarction or otherwise known as cardiac enzymes (CE). Unfortunately only 15-20% of patients presenting with chest pain are ever diagnosed with ACS and up to 10% of patients with eventual myocardial infarction (MI) are misdiagnosed and inappropriately sent home. This is due to the delay in the pathophysiological manifestation of ACS, from arterial occlusion to overt ECG changes and/or CE rise, the heterogeneity of its symptom manifestation which is dependent on the patients' age, gender and any underlying comorbidities, such diabetes mellitus which may delay and/or attenuate the symptoms and the lack of a holistic investigative modality that is able to quickly confirm the diagnosis of ACS/MI and thus expedite intervention.

Cardiovascular magnetic resonance (CMR) is unique in that it offers high spatial resolution enabling a detailed volume and functional assessment, excellent tissue characterisation in any tomographic plane and exceptional prognostic ability which is afforded by late gadolinium enhancement (LGE). Furthermore, radiation free examination also affords the CMR with the ability to incorporate extensive imaging protocols and repeated imaging necessary for both clinical and research imperatives. Studies have already shown that CMR techniques such as myocardial volume and function, perfusion imaging and LGE is able to provide a more accurate diagnosis of ACS compared with standard clinical assessment that includes ECG and CE.

In this thesis, our aims were to address some of these concerns through utillisation of novel imaging techniques advancing the utility of CMR as an important imaging modality in the assessment of ACS. Specifically we planned to look into two major areas of interest, diastolic dysfunction assessment and myocardial characterisation through T1 mapping.

Our first paper discussed the importance of accurate early diagnosis of patients presenting with chest pain and the need for an imaging modality that would serve as a 'one-stop-shop' towards diagnosing ACS. We discussed the move away from conventional methods of assessing ACS and the non-invasive imaging modalities available currently. We discussed the pros and cons of several imaging modalities, notably echocardiography and computed tomography based imaging. We then discussed the many different imaging techniques availed by CMR. We surmised that its ability to accurately and reliably diagnose, risk stratify and prognosticate ACS affords us with a comprehensive investigative tool for assessing patients who present to the Emergency department with chest pain.

Our second paper looked at the utility of assessing diastolic dysfunction as a means of identifying coronary artery occlusion. We discussed its presence signifying one of the earliest signs associated with coronary artery occlusion and the various imaging techniques available to assess it. Echocardiography, being the principal assessment tool for the identification of diastolic dysfunction has several disadvantages namely anatomical impediments to complete endocardial definition, inter-observer variability and lack of tissue characterisation. CMR however offers a more comprehensive assessment of diastolic dysfunction with the introduction of phase-contrast, velocity-encoded imaging and myocardial tagging. We also discussed the possibility of introducing a novel myocardial characterisation technique, T1 mapping and its possible relationship with regional diastolic dysfunction as an indicator of underlying ischaemia or infarction.

Our first step was to evaluate the use of phase-contrast velocity-encoded imaging in the assessment of transmitral flow and the heterogenous contour size and locations used for its assessment. To achieve this we compared the planimetry of the entire left ventricular annulus inflow, the mitral valve leaflet orifice and the mid-mitral valve inflow area, all techniques utilised in many previous studies in assessing transmitral inflow. In confirming the most accurate and reproducible technique, we would then be in a position to be able to confidently use this technique in all subsequent assessments utilised in our study. We have found that CMR derived E wave, A wave and E/A ratio can vary substantially according to planimetric contour location used. We have also established that the greatest degree of agreement, correlation and reproducibility is observed with mitral valve leaflet orifice, which is detailed in our third paper.

We then proceeded with the comprehensive evaluation of global diastolic dysfunction through phase-contrast velocity-encoded imaging and compared it to the current standard - echocardiogram, which is the subject of our fourth paper. We compared the CMR assessment of E/A, S/D and E/E' assessed through phase-contrast velocity-encoded assessment of transmitral flow, pulmonary vein flow and mitral annular velocities against doppler echocardiogram. We found that CMR evaluation of diastolic function with mitral/pulmonary flow and mitral annular velocity is readily achievable, reproducible and demonstrates significantly positive correlation with echocardiogram.

This was important to establish for two reasons. Firstly, previous assessments of diastolic dysfunction utilised different imaging modalities inclusive of echocardiogram, computed tomography and CMR and did not thoroughly assess all three aforementioned indices in each of their studies. Secondly, before we could proceed with CMR assessment of regional diastolic dysfunction, we needed to be sure that the CMR assessment of global left ventricular diastolic dysfunction is comparable to the reference standard, echocardiogram.

In clinical practice, diastolic dysfunction precedes systolic dysfunction, electrocardiographic abnormalities and angina in the pathophysiological cascade following coronary artery occlusion. However, visual estimation of diastolic dysfunction through left ventricular motion abnormality and T2-weighted oedema imaging is subjective and requires extensive clinical experience. Therefore, the development of a noninvasive and quantitative method for detecting coronary artery stenosis through T1 mapping and diastolic circumferential strain analysis of the affected segments would simplify the screening process and ensure early diagnosis, thereby guaranteeing speedy intervention and thus limit the complications post-MI.

To this end, our final study looked at comparing the assessment of myocardial characterisation through pre-contrast T1 relaxation post-ACS, with the CMR measure of regional diastolic dysfunction via left ventricular, segmental diastolic circumferential strain analysis. To our knowledge, no such study has ever been done. Segmental scarring and oedema post MI is known to impair segmental myocardial relaxation and increase myocardial stiffness thereby causing regional diastolic dysfunction. Similarly, scarring and oedema prolongs T1 relaxation in humans. Intuitively, there should be a significantly positive correlation between measures of segmental diastolic function and T1 relaxation post MI. However, several studies have shown poor correlation between measures of global diastolic function and T1 relaxation of infarcted segments post MI. We have found similarly, however when we compared the diastolic circumferential strain analysis with T1 relaxation times of the same infarcted segments, we found a significantly positive correlation with a good degree of agreement and excellent reproducibility.

Therefore in summary, we have been able to demonstrate that the multidimensional CMR assessment of diastolic dysfunction is practicable, easily achievable, readily reproducible and adds a further discriminating value to CMR assessment of ACS. This thesis identifies the strengths and weaknesses of the techniques utilised in CMR assessment of diastolic dysfunction and allows us to use them more appropriately in future. Future work stemming from this thesis is already in the pipeline and will look into the use of other measures of myocardial scarring, oedema and haemorrhage such as T2W and T2* imaging, each independently associated with infarct size and prognosis post MI, and their possible relationship to either global or regional diastolic function.